PATENT COOPERATION TREATY

PCT

INTERNATIONAL PRELIMINARY REPORT ON PATENTABILITY

(Chapter II of the Patent Cooperation Treaty)

(PCT Article 36 and Rule 70)

Applicant's or agent's file reference ON/4-33258A	**FOR FURTHER ACTION**	See Form PCT/IPEA/416
International application No. PCT/EP2004/007437	International filing date *(day/month/year)* 07.07.2004	Priority date *(day/month/year)* 08.07.2003
International Patent Classification (IPC) or national classification and IPC C07D498/18, A61K31/436, A61P19/00		
Applicant NOVARTIS AG		

1. This report is the international preliminary examination report, established by this International Preliminary Examining Authority under Article 35 and transmitted to the applicant according to Article 36.
2. This REPORT consists of a total of 7 sheets, including this cover sheet.
3. This report is also accompanied by ANNEXES, comprising:
   a. ☐ *sent to the applicant and to the International Bureau)* a total of sheets, as follows:
      ☐ sheets of the description, claims and/or drawings which have been amended and are the basis of this report and/or sheets containing rectifications authorized by this Authority (see Rule 70.16 and Section 607 of the Administrative Instructions).
      ☐ sheets which supersede earlier sheets, but which this Authority considers contain an amendment that goes beyond the disclosure in the international application as filed, as indicated in item 4 of Box No. I and the Supplemental Box.
   b. ☐ *(sent to the International Bureau only)* a total of (indicate type and number of electronic carrier(s)) , containing a sequence listing and/or tables related thereto, in computer readable form only, as indicated in the Supplemental Box Relating to Sequence Listing (see Section 802 of the Administrative Instructions).

4. This report contains indications relating to the following items:

☒	Box No. I	Basis of the opinion
☐	Box No. II	Priority
☒	Box No. III	Non-establishment of opinion with regard to novelty, inventive step and industrial applicability
☐	Box No. IV	Lack of unity of invention
☒	Box No. V	Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement
☐	Box No. VI	Certain documents cited
☐	Box No. VII	Certain defects in the international application
☒	Box No. VIII	Certain observations on the international application

Date of submission of the demand	Date of completion of this report
16.04.2005	02.09.2005
Name and mailing address of the international preliminary examining authority: European Patent Office - Gitschiner Str. 103 D-10958 Berlin Tel. +49 30 25901 - 0 Fax: +49 30 25901 - 840	Authorized Officer Baurand, P Telephone No. +49 30 25901-333

INTERNATIONAL PRELIMINARY REPORT ON PATENTABILITY

International application No.
PCT/EP2004/007437

Box No. I Basis of the report

1. With regard to the **language**, this report is based on the international application in the language in which it was filed, unless otherwise indicated under this item.

   ☐ This report is based on translations from the original language into the following language , which is the language of a translation furnished for the purposes of:
   - ☐ international search (under Rules 12.3 and 23.1(b))
   - ☐ publication of the international application (under Rule 12.4)
   - ☐ international preliminary examination (under Rules 55.2 and/or 55.3)

2. With regard to the **elements*** of the international application, this report is based on *(replacement sheets which have been furnished to the receiving Office in response to an invitation under Article 14 are referred to in this report as "originally filed" and are not annexed to this report)*:

   Description, Pages

   1-7 as originally filed

   Claims, Numbers

   1-8 as originally filed

   ☐ a sequence listing and/or any related table(s) - see Supplemental Box Relating to Sequence Listing

3. ☐ The amendments have resulted in the cancellation of:
   - ☐ the description, pages
   - ☐ the claims, Nos.
   - ☐ the drawings, sheets/figs
   - ☐ the sequence listing *(specify)*:
   - ☐ any table(s) related to sequence listing *(specify)*:

4. ☐ This report has been established as if (some of) the amendments annexed to this report and listed below had not been made, since they have been considered to go beyond the disclosure as filed, as indicated in the Supplemental Box (Rule 70.2(c)).
   - ☐ the description, pages
   - ☐ the claims, Nos.
   - ☐ the drawings, sheets/figs
   - ☐ the sequence listing *(specify)*:
   - ☐ any table(s) related to sequence listing *(specify)*:

   * *If item 4 applies, some or all of these sheets may be marked "superseded."*

INTERNATIONAL PRELIMINARY REPORT ON PATENTABILITY

International application No.
PCT/EP2004/007437

Box No. III Non-establishment of opinion with regard to novelty, inventive step and industrial applicability

1. The questions whether the claimed invention appears to be novel, to involve an inventive step (to be non-obvious), or to be industrially applicable have not been examined in respect of:

☐ the entire international application,

☒ claims Nos. 4,5

because:

☒ the said international application, or the said claims Nos. 4,5 (with respect to industrial applicability) relate to the following subject matter which does not require an international preliminary examination (specify):

see separate sheet

☐ the description, claims or drawings *(indicate particular elements below)* or said claims Nos. are so unclear that no meaningful opinion could be formed *(specify)*:

☐ the claims, or said claims Nos. are so inadequately supported by the description that no meaningful opinion could be formed.

☐ no international search report has been established for the said claims Nos.

☐ the nucleotide and/or amino acid sequence listing does not comply with the standard provided for in Annex C of the Administrative Instructions in that:

the written form	☐	has not been furnished
	☐	does not comply with the standard
the computer readable form	☐	has not been furnished
	☐	does not comply with the standard

☐ the tables related to the nucleotide and/or amino acid sequence listing, if in computer readable form only, do not comply with the technical requirements provided for in Annex C-*bis* of the Administrative Instructions.

☐ See separate sheet for further details

Box No. V Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

1. Statement

Novelty (N)	Yes:	Claims	5
	No:	Claims	1-4,6-9
Inventive step (IS)	Yes:	Claims	5
	No:	Claims	1-4,6-9
Industrial applicability (IA)	Yes:	Claims	1-3,6-9
	No:	Claims	-

2. Citations and explanations (Rule 70.7):

see separate sheet

Box No. VIII Certain observations on the international application

The following observations on the clarity of the claims, description, and drawings or on the question whether the claims are fully supported by the description, are made:

see separate sheet

Re Item III.

3.1 Claims 4 and 5 relate to subject-matter considered by this Authority to be covered by the provisions of Rule 67.1(iv) PCT. Consequently, no opinion will be formulated with respect to the industrial applicability of the subject-matter of these claims (Article 34(4)(a)(I) PCT).

Re Item V.

5.1 The following documents are referred to in this communication:

D1: US-A-5 258 389 (GOULET MARK ET AL) 2 November 1993 (1993-11-02)

D2: US-A-5 527 907 (OR YAT S ET AL) 18 June 1996 (1996-06-18)

D3: SHUI C ET AL: "The immunosuppressant rapamycin, alone or with transforming growth factor-beta, enhances osteoclast differentiation of RAW264.7 monocyte-macrophage cells in the presence of RANK-ligand." CALCIFIED TISSUE INTERNATIONAL, vol. 71, no. 5, November 2002 (2002-11), pages 437-446, XP002299513 ISSN: 0171-967X

D4: ROMERO DAVID F ET AL: "Rapamycin: A bone sparing immunosuppressant?" JOURNAL OF BONE AND MINERAL RESEARCH, vol. 10, no. 5, 1995, pages 760-768, XP008036532 ISSN: 0884-0431

D5: VAN ETTEN EVELYNE ET AL: "Analogs of 1,25-dihydroxyvitamin D3 as dose-reducing agents for classical immunosuppressants" TRANSPLANTATION (BALTIMORE), vol. 69, no. 9, 15 May 2000 (2000-05-15), pages 1932-1942, XP008036525 ISSN: 0041-1337

5.2 The present application does not meet the criteria of Article 33(1) PCT, because the subject-matter of claims 1 - 4 and 6 - 9 is not new in the sense of Article 33(2) PCT.

Documents **D1** and **D2** disclose rapamycin and its derivatives which have an identical chemical formula to the claimed compounds, as well as the use of these compounds for the treatment of bone diseases, such as osteoporosis (D1: claim 1; column 24, lines 31 - 32; D2: claim 1; column 90, line 13).

D3 reports that rapamycin directly enhances osteoclastogenesis (page 444, last

paragraph).

These documents are therefore considered to be relevant for novelty of the subject-matter of claims 1, 2, 4 and 6 - 9.

D5 shows that rapamycin and 1,25-dihydroxy-vitamin D_3 exhibit a synergistic immunomodulatory effect (page 1932, left-hand column). Thus, it destroys novelty of claims 3, 6 and 7.

5.3 The present application does not meet the criteria of Article 33(1) PCT, because the subject-matter of claims 1 - 4 and 6 - 9 does not involve an inventive step in the sense of Article 33(3) PCT.

It is well known in the state of the art that rapamycin and its derivatives are potent immunomodulators.

The present application differs in that rapamycin and its derivatives are used for the treatment of bone loss.

The problem to be solved by the present application may be regarded as providing for compounds useful in the treatment of bone loss.

However, the solution to this problem is disclosed in the document **D4** which reports that in contrast to other immunomodulators which cause osteoporosis, rapamycin may be bone sparing (page 766, right-hand column). This view is further supported by **D3** which shows that rapamycin directly enhances osteoclastogenesis (page 444, left-hand column, last paragraph). In view of the above documents, the skilled person would therefore regard the use of rapamycin as an obvious option in order to solve the problem posed.

5.4 For the assessment of the present claims 4 and 5 on the question whether they are industrially applicable, no unified criteria exist in the PCT Contracting States. The patentability can also be dependent upon the formulation of the claims. The EPO, for example, does not recognize as industrially applicable the subject-matter of claims to the use of a compound in medical treatment, but may allow, however, claims to a known compound for first use in medical treatment and the use of such a compound for the manufacture of a medicament for a new medical treatment.

Re Item VIII.

8.1 The terms "**prodrug**" (used in claims 1, 2 and 4), "**analogue**", "**derivative**" and "**fragment**" (claims 3 and 5) are vague and unclear and leave the reader in doubt as to the meaning of the technical features to which they refer, thereby rendering the definition of the subject-matter of said claims unclear (Article 6 PCT).

8.2 Furthermore, it is noted that the terms "**bone resorption inhibitor**", "**partial estrogen agonist**", "**selective estrogen receptor modulator**", "**cathepsin K inhibitor**", "**PTH releaser**" and "**selective androgen receptor molecule**" (claims 3 and 5) meet clarity requirements of Article 6 PCT. However, these terms are objected for lack of support and disclosure, the objection being that the applicant, whilst claiming all ways of achieving the result has provided support and disclosure within the meaning of Article 5 and 6 PCT for only a small number of ways. Such claims are not supported over their whole breadth, and are not disclosed over their whole breath.